REMARKS

Claim 2 has been cancelled and Claim 12 has been amended. No new matter has been added.

Rejections under 35 USC §103

Claims 1, 2, 11 - 13, 16, 19 and 20 stand rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Bissett et al. (WO 95/24785) in view of Perricone (US 2002/0013361) and Claims 1, 2, 11 - 14, 16, 19 and 20 stand rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Bissett et al. and Perricone further in view of the purpura entry from DermNet NZ.

On page 4 of the Final Office Action the Examiner states:" Applicants have not addressed why it would not be obvious to one of ordinary skill in the art to treat rosacea using a different compound known in the art to reduce free radical damage". The compounds of the present invention are iron cheltors. They may also act to reduce free radical damage. The Examiner has not established that SMD pathologies are generated by free radical damage nor has the Examiner provided any evidence that all compounds known to reduce free radical damage would work to treat SMD. While a compound that works to reduce free radical damage may also work to treat SMD a skilled worker would not expect all compounds that reduce free radical damage to also treat SMD.

Likewise, on page 12 of the Office Action the Examiner suggest that agents known in the art to treat free radical damage would be efficacious in treating a wide variety of conditions.

Other than mere allegation, the Examiner has not provided any evidence that all agents

that reduce free radical damage would work to treat SMD. Absent evidence to the contrary, a skilled worker would not expect that agents that are known to reduce free radical damage would work as well as (or the same as) an agent that is also an iron-chelator in treating SMD.

Bissett et al. (WO 95/24785) discloses numerous compounds for the treatment of free-radical damage. One such compound may be 1,2-dimethyl-3hydroxy-pyrid-4-one (i.e., deferiprone). Bissett teaches that free radicals in mammalian cells may arise from environmental sources such as smoke, pollution and radiation. (See page 1, lines12-14). In addition, Bissett teaches that free radicals play a role in HIV. See page 1, lines 23-25. The compounds may be delivered orally, topically or by injection. See pages 6, 7 and 8. The active ingredients are iron chelating compounds that reduce the level of free radicals in mammalian cells (p 1, line 8 - 10).

Perricone (US 2002/0013361) discloses that lipoic acid is useful to treat rosacea. Perricone does not teach or suggest that lipoic acid is an iron chelator. Furthermore, Perricone does not teach or suggest a hydroxypyridonone compound of formulae (I-III).

The web pages from DermNet NZ concern several of the diseases claimed in the method of the present invention. The reference relates to the etiopathological causes of select skin microcirculatory disorders (SMD). In particular, DermNet NZ teaches that the different types of purpura are caused by the destruction of platelets, drugs, infections, certain diseases, damage to small blood vessels, increase of the intraluminar pressure, deficient vascular support or disseminated intravascular coagulation. DermNet NZ also teaches that vasculitis is caused by direct injury to the vessels wall by bacteria or viruses, by activation of antibodies or by the activation of complement. In addition, DermNet NZ teaches that capillaritis arises as a reaction to a medication, to a reaction to some drugs; or a reaction to food additive or viral infections.

There is no indication that any of these SMD pathologies are generated by free radical damage or a problem arising from the presence of an excess of iron. Accordingly, a skilled

worker having knowledge of the etiopathology discussed above, would not try to treat said diseases with a compound of formula I-III (e.g., deferiprone) which is known to be an iron chelator. Furthermore, the DermNet NZ reference suggests treatments for said pathologies. For Purpura the reference teaches that the underlying cause of purpura should be identified and treated accordingly. For vasculitis the reference teaches a skilled worker to treat the underlying infection; discontinue medications such as corticosteroids, colchicine; dapsone or hydroxychloroquine. For capillaritis the reference suggests the removal of the possible cause, such as a food additive or a medication and recommends topical steroids or graduated compression elastic hose. Nowhere in the DermNet NZ reference is there any suggestion that the application of an iron chelator (e.g., deferiprone) would be successful in the treatment of SMD's. A skilled worker would not expect that a compound of formula I-III, such as deferiprone, would be successful in the treatment of SMD's such as vasculitis, capillaritis and similar pathologies.

Bissett teaches treatment of free radical damage from e.g. smoke or radiation and not treatment of SMD's. Perricone discloses that lipoic acid is useful to treat rosacea. Perricone does not teach or suggest that lipoic acid is an iron chelator. Furthermore, Perricone does not teach or suggest a hydroxypyridonone compound of formulae (I-III). Consequently, a skilled worker would have no motivation to combine Bissett et al or Perricone in order to use deferiprone in the treatment of SMD's. There is no correlation between lipoic acid and deferiprone, an iron chelator. Likewise, a skilled artisan would find no suggestion in DermNet NZ for the use of an iron chelator in the treatment of vasculitis, purpura and capillaritis. On the contrary, a skilled worker would have thought that deferiprone was not able to treat said diseases, as it does not interfere in any of the etiopathological causes thereof.

Claims 1-5, 11 - 14, 16, 19 and 20 stand rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Ghisalberti et al. (WO 01/17497) in view of Murad (US 6,630,163).

Neither Ghisalberti nor Murrad provide any suggestion or teaching that would lead a skilled worker to try a compound of formula I-III (i.e, iron chelators) for the treatment of pathologies whose etiopathologies are in no way linked to free radical damage or to the presence of an excess of iron.

Ghisalberti ('497) describes a cosmetic and/or dermatological composition and a method for the treatment and/or prevention of hyperpigmented skin. Ghisalberti's composition may comprise 3-hydroxypyr(id)one derivatives.

Ghisalberti is entirely directed to the treatment of pathologies resulting from an impairment of the activity of melanocytes, such as the increased production of melanin resulting in hyperpigmentation. As noted above in the DermNet NZ reference, which discusses the pathologies of certain SMD's, the claimed pathologies are not in any way related to the production of melanin resulting in hyperpigmentation.

On page 3, lines 10-11 of Ghisalberti states: "the formation of pigmentary spots may result from the combination of blood extravasation around the injection site". However, blood fluid leakage at an injection site is not the result of a pathology caused by a skin microcirculatory disorder. Injection site blood is a side effect of a punctured blood vessel. Furthermore, the hemoglobin in injection site blood leakage is promptly bound to dermal and connective proteins forming hemosiderin deposits, which in turn may stimulate the activity of the surrounding melanocytes. A skilled worker would recognize that spots that are hemosiderinic in nature do not arise from microcirculatory disorders but rather hemosiderin spots are the result of increased production of melanin.

Ghisalberti is silent regarding the treatment of skin microcirculatory disorders. Ghisalberti is particularly silent regarding treatment of purpura, cutaneous vasculitis, itching purpura, purpura annularis telangiectodes, contact allergy skin capillaritis, traumatic skin hemorrhage or actinic purpura.

Thus, Ghisalberti only deals with the treatment of hyperpigmented skin which

results from excess of melanin and/or by hemosiderin deposits, thus making the skin turn to a brown color. Spots that are hemosiderinic in nature do not arise from microcirculatory bleeding. Pathologies caused by skin microcirculatory disorders are not similar to the hyperpigmentation disorders disclosed in Ghisalberti and as the DermNet NZ reference discussed above makes clear, the etipathologies of SMD's are not the result of hyperpigmentation. Thus, a skilled worker would not look towards a hyperpigmentation treatment to treat SMD's.

Murad et al. (US 6,630,163) teaches the use of fruit extracts for neutralizing free radicals. Murad does not teach or suggest iron chelators. At col. 7, line 65 to Col. 8, line 12 Murad lists numerous etiologically different dermatological disorders that may be treated with fruit extracts.

> "The term "dermatological conditions," as used herein, means conditions present anywhere on the skin caused by aging or extrinsic factors such as sunlight, radiations, air pollution, wind, cold, dampness, heat, chemicals, smoke, and smoking. Dermatological conditions include, but are not limited to, dry skin; dandruff; warts; acne; keratosis; psoriasis; eczema; pruritus; age spots; reduced skin moisture; spider veins; senile purpura; lentigines; melasmas; deepening of skin lines; blotches; wrinkles; blemished skin; nodules; atrophy; rosacea; impetigo; precancerous lesions; elastotic changes characterized by leathery, course, rough, dry and yellowish skin; telangiecatic skin; hyperpigmented skin; hyperkeratotic skin; nail infections; inflammatory dermatoses; and damage to hair including, but not limited to, hair breakage, weathering damage, and thinning of hair. "

Thus, the reference broadly teaches a method for treating almost any dermatological disorder. Included in the list are some microcirculatory skin disorders such as senile purpura. The list also includes hyperpigmented skin. Whatever its merits, Murad does not teach that an agent useful for treating hyperpigmented skin is useful for treating microcirculatory skin disorders, and vice versa. Its disclosure is limited to fruit extracts. Fruit extracts are not known to be iron chelators. There is no rationale for extrapolating Murad's teaching to the agents recited in the claims, nor is there any basis in fact for doing so.

Furthermore, according to '163 the fruit extracts can be used to treat any dermatological disorder due to the anti- free radical properties of the extracts. Thus, a variety of pathologies or

very different etiology can allegedly be "treated". The '163 patent makes incredible claims regarding its antioxidant fruit extracts, but a skilled worker would recognize that one agent can not, credibly, be used to treat all the pathologies listed in US 6,630,163.

In other words, contrary to the Examiner allegations, US '163, even in the best case, does not teach a skilled worker that any particular compound, which is normally used to treat hyperpigmentation, can also be used for the treatment of microcirculatory skin disorders such as purpura. A skilled worker would recognize that the mechanisms of action for hyperpigmentation are very different from the mechanisms of action for SMD's.

Thus, in view of the above, it is respectfully requested that the rejections under 35 USC §103 be withdrawn.

Respectfully submitted,

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